IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Jessie L.S. Au, *et al.*
Serial No.	:	09/587,662
Filed:	:	June 5, 2000
For:	:	METHODS AND COMPOSITION FOR MODULATING DRUG ACTIVITY THROUGH TELOMERE DAMAGE
TC/AU	:	1623
Examiner	:	Patrick Lewis
Attorney Docket No.	:	TNI 2-006

HONORABLE COMMISSIONER FOR PATENTS
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DECLARATION UNDER 37 C.F.R. § 1.132

Declarant, Jessie L.-S. Au, does declare and state that:

1. She received her Doctor of Pharmacy and Doctor of Philosophy degrees from the University of California San Francisco, in 1972 and 1980, respectively. She has been on the faculty of The Ohio State University since 1983, rising to the rank of Full Professor in 1992. She has served on multiple government advisory boards (including, *inter alia*, Experimental Therapeutic Study Section, Pharmacology Study Section and Board of Scientific Counselors of the National Institutes of Health, U.S. Army Breast Cancer Program, and Cancer Center Support Grant Review Committee, Manpower Initial Review and Scientific Review Group (Subcommittee D) of the National Cancer Institute). She currently serves on the Developmental Therapeutics Review Committee for the National Cancer Institute. She is also on the Editorial Boards of *Pharmaceutical Research* and *PharmSci*. She received a Research Career Development Award and a Merit Award from the National Cancer Institute, and a Distinguished Scholar Award, the Dorothy M. Davis Chair in Cancer Research, and a Distinguished University Professorship from The Ohio State University. She is a Fellow of the American Association of Advancement of Science and a Fellow of the American Association of Pharmaceutical Scientists. She was Co-director of three research programs (Developmental Therapeutics, Urologic Oncology, Head and Neck Oncology), Director

of Translational Research, and Deputy Director of The Ohio State University Comprehensive Cancer Center, one of the then 28 centers in the U.S. that received such designation from the National Cancer Institute.

2. Her research interests and experience are to develop effective cancer chemotherapy, by identifying effective drugs or combinations of drugs, and by identifying the optimal treatment schedules including the dose and treatment duration. Her work in this area has led to the identification of a new treatment for bladder cancer, for which she has received U.S. Patent No. 6,286,513 B1. This new bladder cancer treatment is based on a new treatment schedule using mitomycin C, a drug that has been used for over 25 years. She and her co-inventor discovered that the prior regimen of administering mitomycin C was less than optimal and subsequently found a new treatment regimen that is nearly twice as effective in human patients, as compared to the prior regimen. She has further determined that suramin, an agent previously used to treat parasitic infections and known to counter growth factor action, enhances the efficacy of cancer chemotherapy when used in low doses. This new therapy, for which she has received U.S. Patent No. 6,599,912 B1, is currently in clinical testing.

3. Similarly, the above-identified patent application teaches a novel method to use existing drugs in a new way.

4. She is an inventor of and co-applicant for the above-identified application.

5. The application discloses that the combination of a telomere damaging agent and a telomerase inhibitory agent is effective in inhibiting or reducing the growth of a cell, or for treating cancer in a patient, even at a subtherapeutic concentrations or doses. Such subtherapeutic concentrations or doses are generally readily determined from the literature. For example, for the agents used, i.e. AZT, d4T, paclitaxel, and docetaxel, the therapeutic doses for their normal therapeutic uses are easily obtained from authoritative sources such as the Physician's Desk Reference, or Mosby's Drug Consult (http://home.mdconsult.com).

6. For AZT, normal therapeutic use ranges from 500-600 milligram per day, taken orally. Knowing that an average 70 kilogram person has a body surface area of approximately 1.73 meter square, a usual therapeutic dosage range would be 289-347 mg/m^2 per day. A subtherapeutic dose would be below this range, for example less then 260 mg/m^2 per day. For d4T, the usual daily dosage is 80 mg per day, which converts to 46.2 mg/m^2 per day for a normal human patient. A subtherapeutic dose of d4T would be below this range, for example less then 40 mg/m^2 per day. For paclitaxel, usual dosages

recommended for patients with several forms of solid tumors range from 135 to 175 mg/m^2 when given as a 3-24 hour infusion, once every three weeks. For administration on a weekly schedule, the usual dosage is 80 mg/m^2. A subtherapeutic dose of paclitaxel would be below this range, for example less than 120 mg/m^2 for administration once every three weeks, and less then 72 mg/m^2 for weekly administration. For docetaxel, the recommended dose is 60-100 mg/m^2 administered intravenously over one hour every three weeks. A subtherapeutic dose would, therefore, be a dose of less than 55 mg/m^2.

7. Based on her general research activities, her education, her knowledge and expertise, and her research on the present invention, it is her considered expert opinion that in general the combination of a telomere damage-inducing agent and a telomerase inhibitory agent at the doses indicated in the above-identified application are effective in inhibiting or reducing the growth of a cell; and specifically further based on the data reported in the above-identified application for paclitaxel and docetaxel as telomere damage-inducing agents and AZT and d4T as telomerase inhibitory agents, that the known vincristine, cisplatin, doxorubicin, mitoxantrone, methotrexate, or 5–fluorouracil telomere damage-inducing agents and carbovir, 7-deaza-dGTP, or 7-deaza-dATP telomerase inhibitory agents, similary are very likely to similary display efficacy in inhibiting or reducing the growth of a cell, as taught in the above-identified application.

8. All statements made herein of her own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

FURTHER DECLARANT SAYETH NAUGHT.

Date September 8, 2004

Jessie L.-S. Au